c) treating said PMBC cells with a regulatory composition comprising TGF- β and irradiated T cell-depleted mononuclear cells from said donor;

d) expanding said PMBC cells following treatment with said regulatory composition ; and

e) introducing said treated PMBC cells to said recipient.

4. (Amended) A method according to claim 2 wherein said regulatory composition further comprises cytokines selected from the group consisting of IL-2 and IL-15.

Please add the following new claims:

5. (New) A method according to claim 1, wherein said PMBCs are enriched for CD4+ T cells.

6. (New) A method according to claim 5 wherein said CD4+ cells are enriched for naive CD4+ T cells.

7. (New) A method according to claim 1, wherein said PMBCs are enriched for CD8+ T cells.

REMARKS

Claims 1-4 are pending in the instant application. Claims 1 and 3 have been canceled. Claim 2 has been amended. Support for amended claim 2 is found in the originally filed claim 3. Claims 5-6 have been added. Support for newly added claim 5 is found on page 11, lines 10-11. Support for newly added claim 6 is found on page 11, lines 18-21. Support for newly added claim 7 is found on page 11, lines 22-23. An "Appendix of Pending Claims" is attached hereto for the Examiner's convenience, as well as a "Version to Show Changes Made."

Rejection Under 35 USC Section 112, first paragraph

Claims 1-4 are rejected under 35 U.S.C. §112, first paragraph, for lack of enablement. Specifically, the Examiner states that the specification does not provide enablement for any regulatory composition or any stimulatory cell.

Claims 1 and 3 have been cancelled. Thus, the rejection is moot as applied to claims 1 and 3.

Without admitting the propriety of the rejection, and reserving the right to pursue broader subject matter in a related case, Claim 2 has been amended to include components of the regulatory composition and to define the source of stimulatory cells. Accordingly, Applicants respectfully request withdrawal of the rejection of claims 1-4 under 35 U.S.C. § 112, first paragraph.

Rejection Under 35 USC Section 112, second paragraph

Claims 1-4 are rejected under 35 U.S.C. §112, first paragraph, for lack of written description. Specifically, the Examiner states that the specification does not provide written description for any regulatory composition or any stimulatory cell.

Claims 1 and 3 have been cancelled. Thus, the rejection is moot as applied to claims 1 and 3.

Without admitting the propriety of the rejection, and reserving the right to pursue broader subject matter in a related case, Claim 2 has been amended to include components of the regulatory composition and to define the source of stimulatory cells. Claim 2 has been amended as described above. Accordingly, Applicants respectfully request withdrawal of the rejection of claims 1-4 under 35 U.S.C. § 112, first paragraph.

Rejections Under 35 USC Section 102(a)

The Examiner has rejected claims 1-4 under 35 USC Section 102(a) as being anticipated by WO 99/45524. Applicants respectfully disagree because WO 99/45524 fails to teach each and every element of claims 1-4.

Claims 1 and 3 have been cancelled. Thus, the rejection is moot as applied to claims 1 and 3.

By way of summary, the present invention is directed to methods of preventing graft rejection in a recipient following organ transplantation. Rejection of solid organ transplants generally occurs when T lymphocytes from the recipient recognize and respond to donor histocompatibility antigens. Thus, the present invention prevents graft rejection by suppressing T cell activation and inducing a tolerant state in the recipient's cells. This is achieved by inducing some of the recipient's cells to assume a surveillance role and prevent other recipient cells from mounting an immune attack against the transplanted organ. The net effect is for the recipient's lymphocytes to become tolerant of the histocompatibility antigens of the donor, thereby making possible the long term survival of the transplanted organ.

WO 99/45524 describes a method for inducing T cell tolerance in hematopoietic stem cells. By inducing tolerance in hematopoietic stem cells, histoincompatible stells cells may be transferred to individuals suffering a variety of malignant or hereditary diseases. Specifically, WO 99/45524 describes methods for treating donor stem cell preparation to prevent the onset of graft versus host disease, a disease in which the transferred T cells turn against the recipient's tissues causing multi-organ dysfunction and destruction.

In contrast, claim 2 describes a method for inducing a recipient's cells to decrease graft rejection by isolating and mixing (*ex vivo*) peripheral mononuclear blood cells (PMBCs) from a recipient and a donor; then treating the cells with TGF- β and irradiated T cell-depleted mononuclear cells then expanding the cells; and finally, introducing these cells to the recipient.

As the Examiner is aware, "[i]t is axiomatic that for prior art to anticipate under § 102 it has to meet every element of the claimed invention." *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367 (Fed. Cir. 1986). The law is well established that in order to anticipate a claim, the prior art must disclose "each and every element"of the claimed invention. *SSIH Equipment S.A.v. U.S. Inc. Int'l. Trade Commission*, 218 USPQ 678, 688 (Fed. Cir. 1983). As stated by the Federal Circuit in *In re Bond*, 15 USPQ2d 1566, 1567 (Fed. Cir. 1990), "[f]or a prior art reference to anticipate in terms of 35 U.S.C. § 102, every element of the claimed invention must be identically shown in a single reference." See also

Glaverbel Societe Anonyme v. Northlake Marketing & Supply, Inc., 33 USPQ2d 1496 (Fed. Cir. 1995).

As discussed above, WO 99/45524 does not explicitly teach or enable the use of a regulatory composition comprising isolating and mixing PMBCs from a recipient and a donor; then treating the cells with TGF- β and irradiated T cell-depleted mononuclear cells as a means for inducing T cell tolerance and ameliorating the rejection of a solid organ transplant. Thus, WO 99/45524 does not anticipate Claims 1- 4. Applicants respectfully request the rejection of Claims 1 -4 under 35 U.S.C. § 102(a)

Rejections Under 35 USC Section 102(b)

The Examiner has rejected claims 1 and 3 under 35 USC Section 102(b) as being anticipated by Halverson *et al.* Without agreeing with the Examiner's conclusion, Applicants note that claims 1 and 3 have been canceled, and hence the rejection is obviated.

Rejections Under 35 USC Section 103(a)

The Examiner has rejected claims 1-4 under 35 USC Section 103(a) as being unpatentable over WO 99/45524 publication (Sept 1999, PTO 892) or Halverson *et al* each in view of Bonig *et al* (Scand J Immunol 50: 612-618, Dec 1999; PTO 892). Applicants respectfully disagree because the prior art and present invention refer to two different immune responses.

Claims 1 and 3 have been cancelled. Thus, the rejection is moot as applied to claims 1 and 3.

As described above, WO 99/45524 teaches methods of inducing T suppressor cells as a means of preventing GVHD. The reason for generating suppressor T cells is because in stem cell transplantation donor T cells are transferred with stem cells for engraftment of the stem cells in the recipient. As some of the transferred T cells can cause GVHD, WO 99/45524 teaches a method to induce certain T cells from a stem cell transplant donor to become suppressor cells that prevent other donor T cells from mounting an immune attack against the recipient.

Halverson teaches a method for generating cytotoxic T cells, i.e., CD8+ Tc1 and Tc2 cells for use in tumor therapy.

Bonig *et al* teaches methods of overcoming the immunosuppressive effects of TFG-β produced by tumors using cytokines. Thus, the methods taught by Bonig are directed toward using cytokines as means of stimulating the immune response against tumors by neutralizing the effect of immunosuppressive mediators, such as TGF-β.

In contrast, the present invention is directed to methods of preventing graft rejection in a recipient following organ transplantation. Rejection of solid organ transplant generally occurs when cytotoxic T cells from the recipient recognize and respond to donor histocompatibility antigens resulting in an immune attack against the graft. The present invention prevents graft rejection by inducing immune tolerance. This is achieved by inducing some of the recipient's T cells to become suppressor cells. These "suppressor" cells assume a surveillance role and prevent other recipient T cells from mounting an immune attack against the graft. Thus, the net effect of the tolerant state in the recipient is long term survival of the graft.

In the present invention, induction of suppressor T cells is done using TGF-β as a novel T cell differentiation factor. Cytokines, such as IL-2 or Il-15, are used to enable TGF-β to develop its growth and differentiation properties.

When rejecting claims under 35 U.S.C. §103, the Examiner bears the burden of establishing a *prima facie* case of obviousness. See, e.g., *In re Bell* 26 USPQ2d 1529 (Fed. Cir. 1993); M.P.E.P. Section 2142. To establish a *prima facie* case, three basic criteria must be met: (1) the prior art must provide one of ordinary skill with a suggestion or motivation to modify or combine the teachings of the references relied upon by the Examiner to arrive at the claimed invention; (2) the prior art must provide one of ordinary skill with a reasonable expectation of success; and (3) the prior art, either alone or in combination, must teach or suggest every limitation of the rejected claims. The teaching or suggestion to make the claimed invention, as well as the reasonable expectation of success, must come from the prior art, not the Applicant's disclosure. *In re Vaeck*, 20 USPQ2d 1438 (Fed. Cir. 1991); MPEP Section 706.02(j). If any one of these criteria is not met, *prima facie* obviousness is not established.

The prior art does not provide one of ordinary skill in the art with a suggestion or motivation to modify or combine the teachings, because one of skill in the art would not combine a method for inducing an immune response either through the generation of cytotoxic T cells or by the neutralization of immunosuppressive mediators, with a method for preventing the generation of cytotoxic T cells because the objectives of the teachings are polarly opposed. That is, the methods of Halverson and Bonig are directed to inducing a immune response, whereas the method of WO 99/45524 is directed to suppressing an immune response in donor stem cells. Thus, Applicants submit that there is no motivation to modify or combine the teachings of Halverson, Boning, and WO 99/45524 to arrive at the present invention, which is directed toward suppressing an immune response in recipient T cells to prevent graft rejection.

Moreover, it is improper to combine references where the references teach away from their combination. See *In re Grasselli*, 713 F.2d 731, 743, 218 USPQ 769,779 (Fed. Cir. 1983) and MPEP § 2145 X. Applicants submit that the beneficial result taught in the present invention, i.e., a method for generating suppressor T cell in a recipient as a means for preventing an immune response against a transplanted organ, is not suggested by combining references that teach methods for inducing an immune response through the induction of cytotoxic T cells with a reference that teaches methods for inhibiting an immune response.

Finally, Applicants note that MPEP § 2143.01 states if the proposed modification would render the prior art invention being modified unsatisfactory for its intended purpose, then there is no suggestion or motivation to make the proposed modification. Applicants submit that by combining the present invention directed to suppressing the immune response against a transplanted organ with the prior art inventions directed toward eliciting an immune response would make the prior art inventions inoperable for there intended purpose which is to induce an immune response to eliminate tumors.

Secondly, Applicants submit that the teaching of the prior art does not provide a person of ordinary skill with a reasonable expectation of success as methods for inducing cytotoxic T cells combined with a method for inhibiting the activation of cytotoxic T cell in donor stem cells are at odds with each other. In other words, one of skill in the art would not

expect to suppress graft rejection by combining methods for inducing graft rejection (i.e, generation of cytotoxic T cells) with methods for preventing graft rejection (i.e., generating suppressor T cells).

Finally, the prior art, either alone or in combination, does not teach or suggest every limitation of the rejected claims. None of the references teaches a method for inducing a tolerant state in a recipient's T cells to decrease graft rejection.

Thus, neither WO 99/45524 nor Halverson nor Bonig alone or in combination, teach or suggest each and every limitation of claims 2 and 4. Accordingly, the Examiner has failed to establish a prima facie case of obviousness against claims 1-4. Applicants respectfully request withdrawal of the rejection under 35 U.S.C. § 103(a).

Attached hereto is a marked-up version of the changes made to the claims by the "Restriction and Amendment". The attached page is captioned **"Version with markings to show changes made."**

Applicants submit that the claims are now in condition for allowance and early notification to that effect is respectfully requested. Please direct any calls in connection with this application to the undersigned at (415) 781-1989.

Dated: 5/28/02

Respectfully submitted,

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"VERSION WITH MARKINGS TO SHOW CHANGES MADE"

Claim 1 has been cancelled.

Claim 2 has been amended as follows:

2. (Amended) A method for inducing a recipient's cells to decrease graft rejection comprising:

a) isolating peripheral mononuclear blood cells (PMBCs) from a recipient and a donor;

b) mixing donor and recipient PMBC cells *ex vivo*;

c) treating said PMBC cells with a regulatory composition comprising TGF- β and irradiated T cell-depleted mononuclear cells from said donor;

d) expanding said PMBC cells following treatment with said regulatory composition ; and

e) introducing said treated PMBC cells to said recipient.

Claim 3 has been cancelled.

4. (Amended) A method according to claim [3]2 wherein said regulatory composition further comprises cytokines selected from the group consisting of IL-2 and IL-15.

Appendix of Pending Claims

2. (Amended) A method for inducing a recipient's cells to decrease graft rejection comprising:

a) isolating peripheral mononuclear blood cells (PMBCs) from a recipient and a donor;

b) mixing donor and recipient PMBC cells *ex vivo*;

c) treating said PMBC cells with a regulatory composition comprising TGF- β and irradiated T cell-depleted mononuclear cells from said donor;

d) expanding said PMBC cells following treatment with said regulatory composition ; and

e) introducing said treated PMBC cells to said recipient.

4. A method according to claim [3]1 wherein said regulatory composition further comprises cytokines selected from the group consisting of IL-2 and IL-15.

5. (New) A method according to claim 2, wherein said PMBCs are enriched for CD4+ T cells.

6. (New) A method according to claim 5 wherein said CD4+ cells are enriched for naive CD4+ T cells.

7. (New) A method according to claim 1, wherein said PMBCs are enriched for CD8+ T cells.